

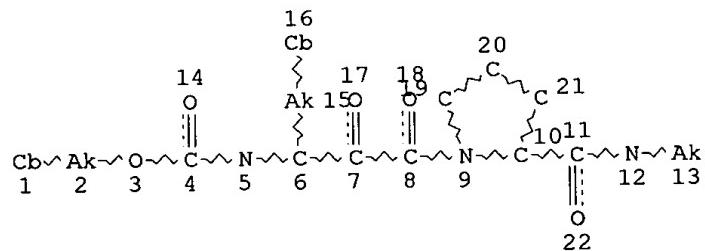
February 11, 2003

L4 ANSWER 9 OF 9 HCPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1992:227702 HCPLUS
 DOCUMENT NUMBER: 116:227702
 TITLE: Intriguing structure-activity relations underlie the potent inhibition of HIV protease by norstatine-based peptides
 AUTHOR(S): Tam, Tim F.; Carriere, Julie; MacDonald, I. David; Castelhano, Arlindo L.; Pliura, Diana H.; Dewdney, Nolan J.; Thomas, Everton M.; Bach, Chinh; Barnett, Jimmy; et al.
 CORPORATE SOURCE: Syntex Res. Canada, Mississauga, ON, L5N 3X4, Can.
 SOURCE: Journal of Medicinal Chemistry (1992), 35(7), 1318-20
 CODEN: JMCMAR; ISSN: 0022-2623
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Phenylnorstatine contg. peptides extending from the P2 to P1' positions, with L-proline at the P1' position and S-stereochem. of the P1 component, exhibit impressive potency vs. HIV-1 potease ($IC_{50} = 0.58\text{--}7.4\text{ nM}$). Representative ketoamides are also active with slightly lower potency. Analogous hydroxyethylamines have previously been reported to be potent inhibitors of this enzyme. The presence of an addnl. carbonyl in this series of proline-based inhibitors enhances their potency, and alters structure-activity relations profoundly. Whereas divergent effects on potency have been obsd. for epimeric hydroxyethylamines upon extension of such P1' terminal peptides to P3' with Ile-Val, lengthening of norstatine contg.-inhibitors in the same fashion, dramatically increases the potency of the R-diastereomer and leaves the IC_{50} of the S-epimer essentially unchanged. Most interestingly, amino acid residues in the P1' position contg. parent and fused piperidines lower activity in the norstatine series. By contrast, significant enhancements in inhibitor potency were reported in the hydroxyethylamine series for such proline replacements. Conformational preferences of 6 member rings influenced by A1,3-strain may contribute to the redn. in potency obsd. for the norstatine contg. peptides.

> d que

L1

STR



NODE ATTRIBUTES:

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CONNECT IS E2 RC AT 2
CONNECT IS E2 RC AT 5
CONNECT IS E2 RC AT 12
CONNECT IS E1 RC AT 13
CONNECT IS E2 RC AT 15
  
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February 11, 2003

DEFAULT MLEVEL IS ATOM
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 DEFAULT ECLEVEL IS LIMITED
 ECOUNT IS E6 C AT 1
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GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
 L3 40 SEA FILE=REGISTRY SSS FUL L1
 L4 9 SEA FILE=HCAPLUS ABB=ON PLU=ON L3

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L4 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2002:676142 HCAPLUS
 DOCUMENT NUMBER: 137:197524
 TITLE: HIV protease inhibitors and their use for treating HIV
 protease-associated diseases
 INVENTOR(S): Wong, Chi-Huey
 PATENT ASSIGNEE(S): The Scripps Research Institute, USA
 SOURCE: PCT Int. Appl., 153 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002068586	A2	20020906	WO 2002-US1695	20020122
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2001-262846P P 20010119				

PRIORITY APPLN. INFO.:

MARPAT 137:197524

OTHER SOURCE(S):

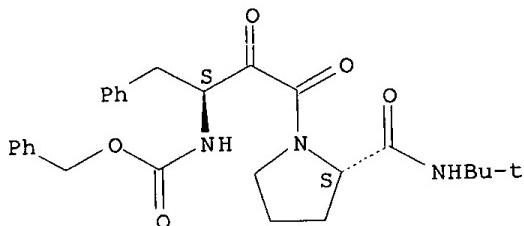
AB With the help of X-ray structural analyses of drug-resistant HIV proteases and mol. modeling, a new type of inhibitor with a small P3 residue has been developed. These inhibitors are effective against HIV and its drug-resistant mutants, as well as FIV. Modification of existing HIV protease inhibitors by reducing the size of the P3 residue has the same effect. This finding provides a new strategy for the development of HIV protease inhibitors effective against the wild type and drug-resistant mutants and further supports that FIV protease is a useful model for drug-resistant HIV proteases, which often are developed through redn. in

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size of the binding region for the P3 group or the combined P3 and P1 groups. The HIV protease inhibitors may be used to treat diseases assocd. with HIV protease, e.g., AIDS.

- IT 141197-75-3P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (HIV protease inhibitors and their use for treating HIV protease-assocd. diseases)
- RN 141197-75-3 HCAPLUS
 CN Carbamic acid, [(1S)-3-[(2S)-2-[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI)
 (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:801933 HCAPLUS
 DOCUMENT NUMBER: 137:226
 TITLE: A study on docking mode of HIV protease and their inhibitors
 AUTHOR(S): Akaho, Eiichi; Morris, Garret; Goodsell, David; Wong, David; Olson, Arthur
 CORPORATE SOURCE: Fac. Pharmaceutical Sci., Kobe Gakuin Univ., 518 Arise, Ikawadani-cho, Nishi-ku, Kobe, 651-2180, Japan
 SOURCE: Journal of Chemical Software (2001), 7(3), 103-114
 CODEN: CHSFEC; ISSN: 0918-0761
 PUBLISHER: Kagaku Sofutowea Gakkai
 DOCUMENT TYPE: Journal
 LANGUAGE: English

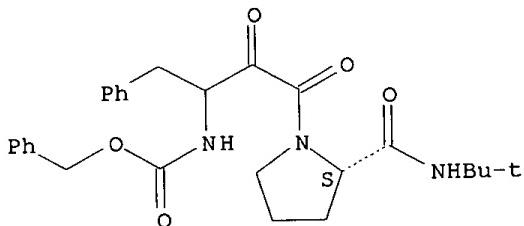
AB The capability to propose feasible ways of binding a putative ligand inhibitor to a known receptor site is crucial to the successful structure-based drug design. A computer docking approach is to position or "dock" ligand and receptor mols. together in many different ways and then score each orientation by applying a reasonable evaluation function. AutoDock3.0 is an unbiased type docking program in which a user does not have to direct a ligand to an active site, but the system finds an optimal position after a ligand is placed in a random manner. Synthesized derivs. of the intact inhibitor (inh1) of HIV protease were investigated for their docking modes as compared with their Ki values. Among the derivs., inh3trans and inh6H were found to be more powerful inhibitors of HIV protease than the others. Gibbs free energy calcd. by applying mol. mechanics interaction energies was compared with the one obtained by using exptl. inhibitory potencies for a series of HIV protease inhibitors, and a fairly good correlation was found between the two. Based on this favorable correlation between the computational and the exptl.

results, the computational expts. were pursued for the compds. drawn by Sybyl taking into consideration the fact that unexploited carbon affinity regions (or hydrophobic regions) with sizable vol. were detected on the docking study of inh1 and inh8 against HIV protease. Those were compds. with a t-Bu substituted by various hydrophobic side chains. Among those a compd. with a benzyl group exhibited the lowest docking energy. Since one of the goals of this paper was to perform the computational drug-design expt. to investigate potential HIV protease inhibitors, the authors would like to leave the clin. investigational work for the expertise of those areas.

IT 191849-89-5 191850-28-9 191850-29-0
 433709-59-2 433709-60-5 433709-61-6
 433709-64-9 433709-65-0
 RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (docking mode of HIV protease and their inhibitors)

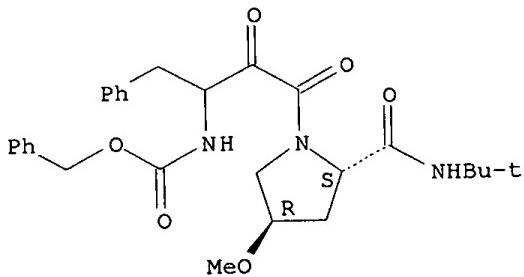
RN 191849-89-5 HCPLUS
 CN Carbamic acid, [3-[(2S)-2-[[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191850-28-9 HCPLUS
 CN Carbamic acid, [3-[(2S,4R)-2-[[[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

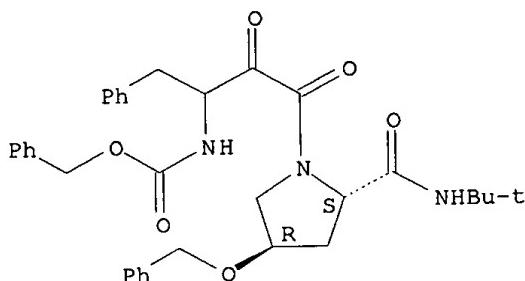
Absolute stereochemistry.



RN 191850-29-0 HCPLUS
 CN Carbamic acid, [3-[(2S,4R)-2-[[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-,

phenylmethyl ester (9CI) (CA INDEX NAME)

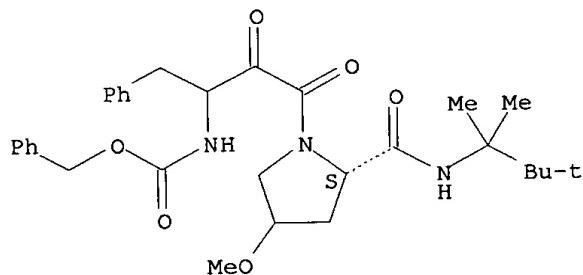
Absolute stereochemistry.



RN 433709-59-2 HCAPLUS

CN Carbamic acid, [3-[(2S)-4-methoxy-2-[(1,1,2,2-tetramethylpropyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

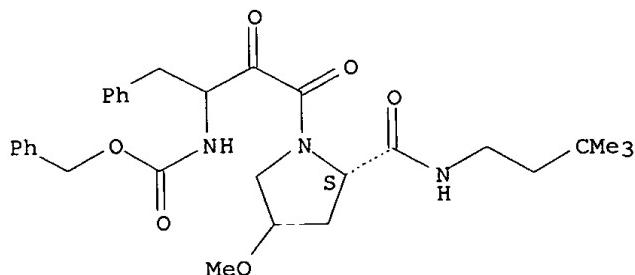
Absolute stereochemistry.



RN 433709-60-5 HCAPLUS

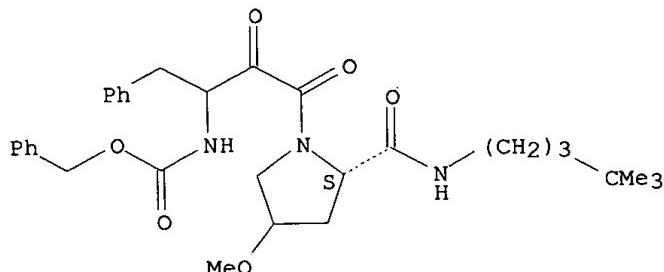
CN Carbamic acid, [3-[(2S)-2-[(3,3-dimethylbutyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



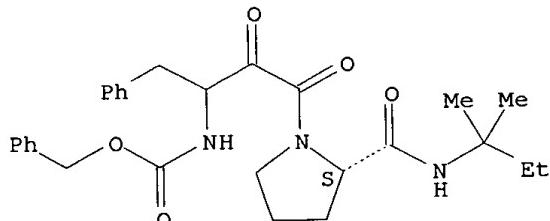
RN 433709-61-6 HCAPLUS
 CN Carbamic acid, [3-[(2S)-2-[[[(4,4-dimethylpentyl)amino]carbonyl]-4-methoxy-
 1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester
 (9CI) (CA INDEX NAME)

Absolute stereochemistry.



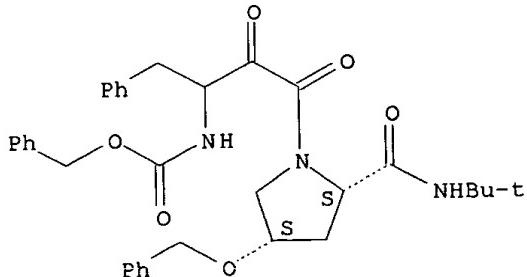
RN 433709-64-9 HCAPLUS
 CN Carbamic acid, [3-[(2S)-2-[[[(1,1-dimethylpropyl)amino]carbonyl]-1-
 pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI)
 (CA INDEX NAME)

Absolute stereochemistry.



RN 433709-65-0 HCAPLUS
 CN Carbamic acid, [3-[(2S,4S)-2-[[[(1,1-dimethylethyl)amino]carbonyl]-4-
 (phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-,
 phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



Meller 09/077,712

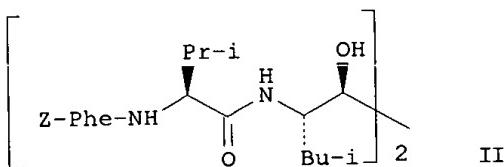
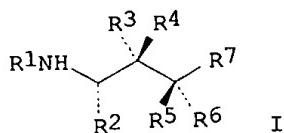
February 11, 2003

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 9 HCPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:390367 HCPLUS
DOCUMENT NUMBER: 131:45104
TITLE: HIV/FIV protease inhibitors having a small P3 residue
INVENTOR(S): Lee, Taekyu; Wong, Chi-Huey; Elder, John H.
PATENT ASSIGNEE(S): The Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9929311	A1	19990617	WO 1998-US25964	19981208
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
AU 9919045	A1	19990628	AU 1999-19045	19981208
EP 1039886	A1	20001004	EP 1998-963800	19981208
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
PRIORITY APPLN. INFO.:			US 1997-67959P	P 19971208
			WO 1998-US25964	W 19981208

OTHER SOURCE(S): MARPAT 131:45104
GI



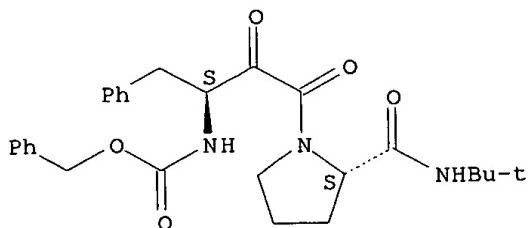
AB Protease inhibitors I [R1 = H, carbobenzyloxy (Z), Z-Val, Z-protected dipeptidyl; R2 = benzyl, isobutyl; R3, R4 H, H; H, OH, O; R5, R6 = H, H; O; R7 = prolinamide or N-tert-butylprolinamide residue] were prepd. Thus, peptidyl diol II was prepd. and showed $K_i = 487 \pm 20$ and 5.5 ± 0.8 for inhibition of FIV PR and HIV PR, resp.

IT 141197-75-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HIV/FIV protease inhibitors having a small P3 residue)

RN 141197-75-3 HCAPLUS

CN Carbamic acid, [(1S)-3-[(2S)-2-[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

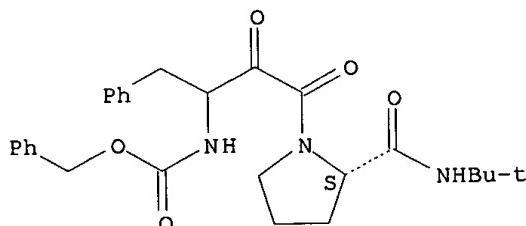
L4 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:73185 HCAPLUS

Meller 09/077,712

February 11, 2003

DOCUMENT NUMBER: 130:276229
TITLE: Development of a New Type of Protease Inhibitors,
Efficacious against FIV and HIV Variants
AUTHOR(S): Lee, Taekyu; Le, Van-Duc; Lim, Dongyeol; Lin,
Ying-Chuan; Morris, Garrett M.; Wong, Andrew L.;
Olson, Arthur J.; Elder, John H.; Wong, Chi-Huey
CORPORATE SOURCE: Department of Chemistry and the Skaggs Institute for
Chemical Biology, The Scripps Research Institute, La
Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1999),
121(6), 1145-1155
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Based on the structural anal. of FIV protease and drug-resistant HIV
proteases and mol. modeling, a new type of inhibitors with a small P3
residue has been developed. These inhibitors are effective against HIV
and its drug-resistant mutants, as well as SIV and FIV. Modification of
existing HIV protease inhibitors by reducing the size of the P3 residue
has the same effect. This finding provides a new strategy for the
development of HIV protease inhibitors effective against the wild-type and
drug-resistant mutants. It further supports the use of FIV protease as a
useful model for drug-resistant HIV proteases, which often have a more
constricted binding region for the P3 group or the combined P3 and P1
groups.
IT 191849-89-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)
(synthesis of a new type of protease inhibitors, efficacious against
FIV and HIV variants)
RN 191849-89-5 HCPLUS
CN Carbamic acid, [3-[(2S)-2-[[[(1,1-dimethylethyl)amino]carbonyl]-1-
pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 9 HCPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:473732 HCPLUS
DOCUMENT NUMBER: 127:81793

Meller 09/077,712

February 11, 2003

TITLE: Preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors

INVENTOR(S): Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen

PATENT ASSIGNEE(S): Scripps Research Institute, USA; Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen

SOURCE: PCT Int. Appl., 202 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

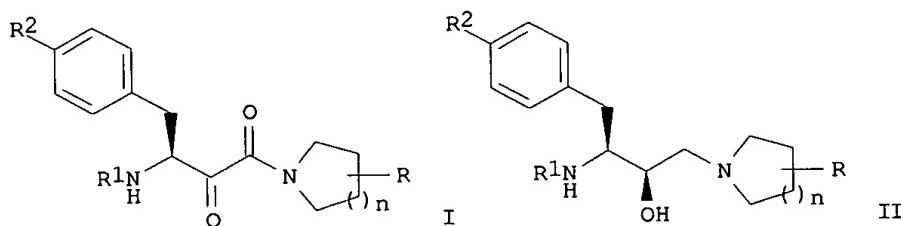
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9721100	A1	19970612	WO 1996-US19571	19961209
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2238337	AA	19970612	CA 1996-2238337	19961209
AU 9712844	A1	19970627	AU 1997-12844	19961209
AU 728373	B2	20010111		
EP 873519	A1	19981028	EP 1996-943657	19961209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2000502332	T2	20000229	JP 1997-521485	19961209
PRIORITY APPLN. INFO.:			US 1995-568532 A2	19951207
			WO 1996-US19571 W	19961209

OTHER SOURCE(S): MARPAT 127:81793
GI



AB Combinatorial libraries of HIV and FIV protease inhibitors are characterized by .alpha.-keto amide or hydroxyethylamine core structures I and II [n = 1, 2; R = one or more groups CONHMe3, CH2OH, CH2OME, CH2OCH2Ph, OH, OCH2Ph, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy, etc.; R1 = PhCH2O2C (Cbz), Me3CO2C (Boc), acyl; R2 = H, HO, PhCH2O, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy] flanked by on one side by substituted pyrrolidines, piperidines, or azasugars and on the other side by Phe, Tyr, or substituted tyrosines. The libraries are synthesized via coupling of the nitrogen heterocycles with hydroxy acids, e.g. III, followed by oxidn. to the keto amide, or a one-step coupling with epoxides, e.g. IV. Highly efficacious drug candidates are identified by screening the libraries for binding and inhibitory activity against both HIV and FIV protease. Drug candidates displaying clin. useful activity against both HIV and FIV protease are identified as being potentially resistive against a loss of inhibitory activity due to development of resistant strains of HIV.

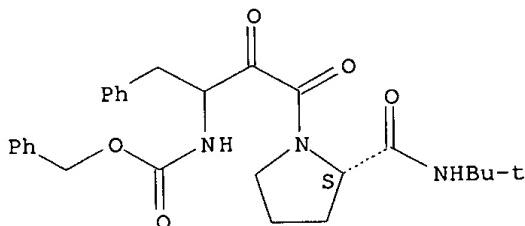
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 191850-35-8P 191850-36-9P 191850-37-0P
 191850-38-1P 191850-59-6P 191850-60-9P
 191850-61-0P 191850-91-6P 191850-92-7P
 191850-93-8P 191850-94-9P 191850-95-0P
 191850-96-1P 191851-37-3P 191851-40-8P
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prep. of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

RN 191849-89-5 HCAPLUS

CN Carbamic acid, [3-[2-(2S)-2-[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester (9CI) (CA INDEX NAME)

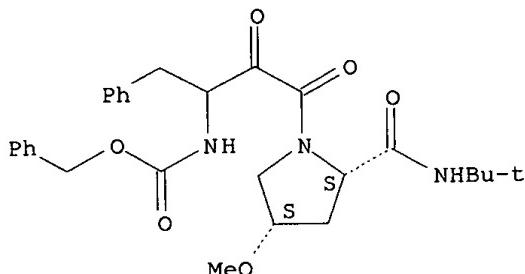
Absolute stereochemistry.



RN 191850-27-8 HCAPLUS

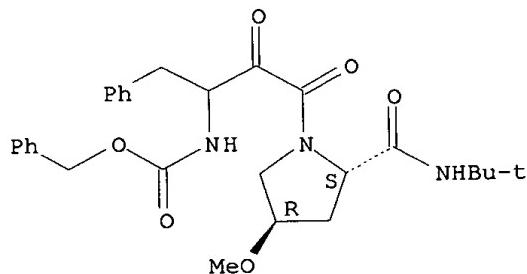
CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2S-(2.alpha.,4.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



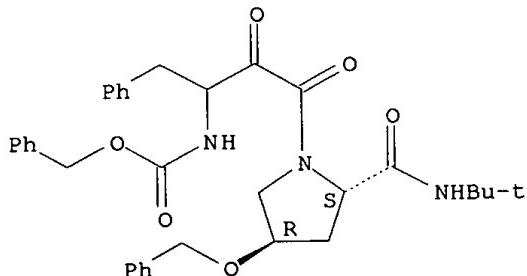
RN 191850-28-9 HCAPLUS
 CN Carbamic acid, [3-[(2S,4R)-2-[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



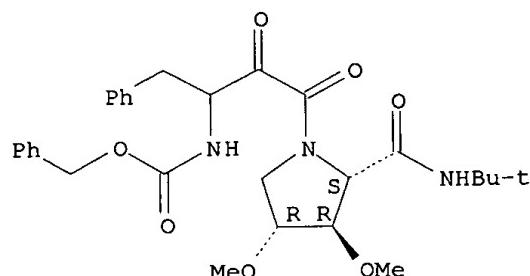
RN 191850-29-0 HCAPLUS
 CN Carbamic acid, [3-[(2S,4R)-2-[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



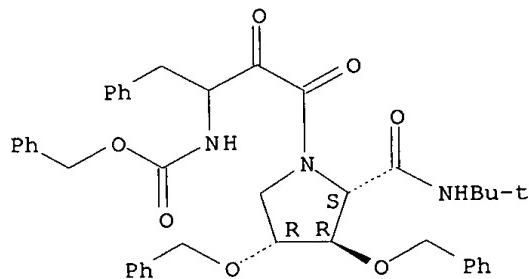
RN 191850-30-3 HCAPLUS
 CN Carbamic acid, [3-[(2-[(1,1-dimethylethyl)amino]carbonyl)-3,4-dimethoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



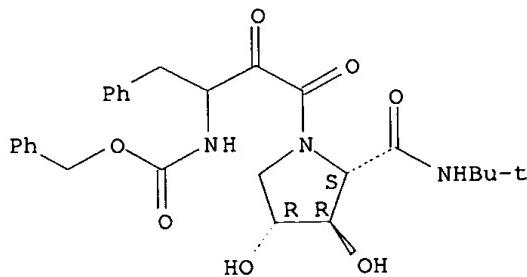
RN 191850-31-4 HCPLUS
 CN Carbamic acid, [3-[2-[(1,1-dimethylcethyl)amino]carbonyl]-3,4-bis(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



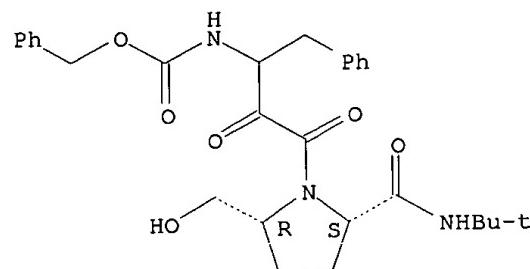
RN 191850-32-5 HCPLUS
 CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-3,4-dihydroxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



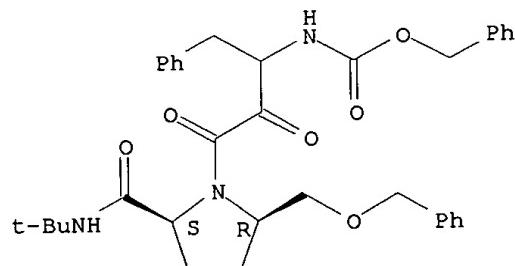
RN 191850-33-6 HCPLUS
 CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-5-(hydroxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



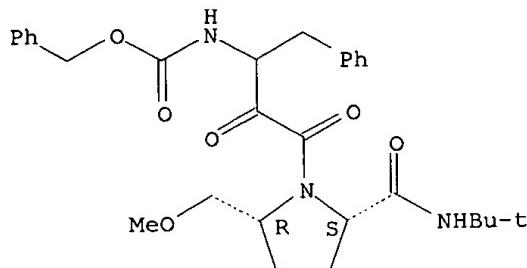
RN 191850-34-7 HCPLUS
 CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-5-[(phenylmethoxy)methyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



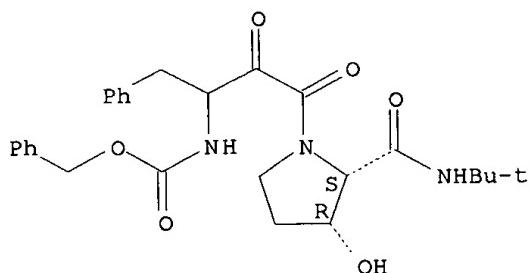
RN 191850-35-8 HCPLUS
 CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



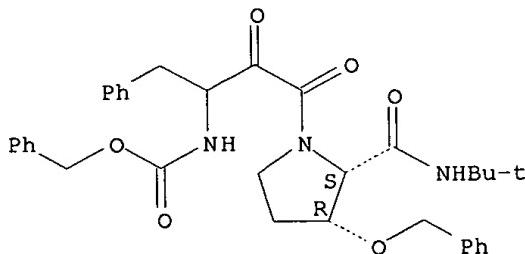
RN 191850-36-9 HCAPLUS
CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-3-hydroxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester,
[2S-(2.alpha.,3.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



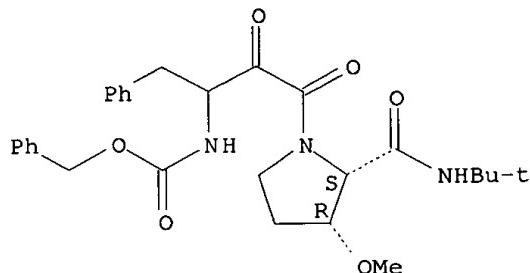
RN 191850-37-0 HCPLUS
CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-3-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191850-38-1 HCPLUS
CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-3-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester,
[2S-(2.alpha.,3.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

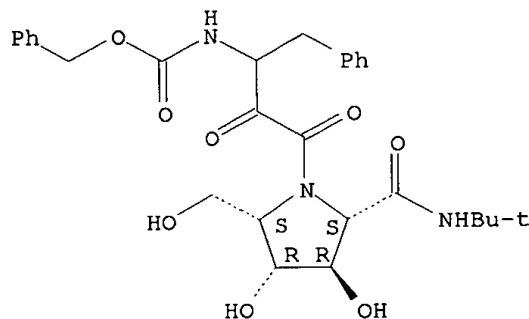
Absolute stereochemistry.



RN 191850-59-6 HCAPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-3,4-dihydroxy-5-(hydroxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

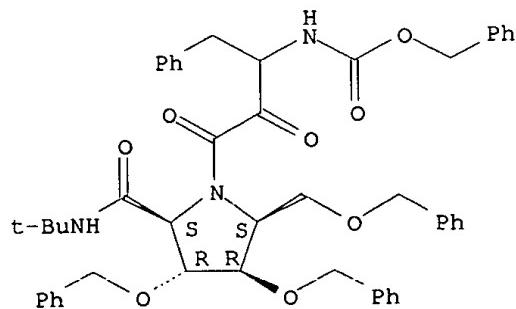
Absolute stereochemistry.

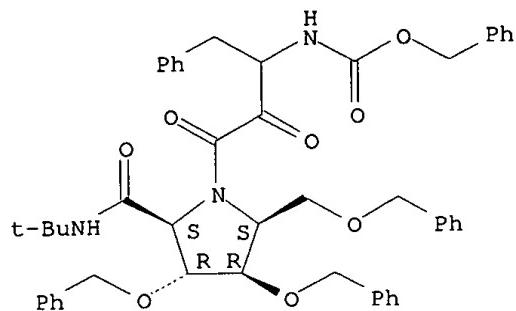


RN 191850-60-9 HCAPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-3,4-bis(phenylmethoxy)-5-[(phenylmethoxy)methyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

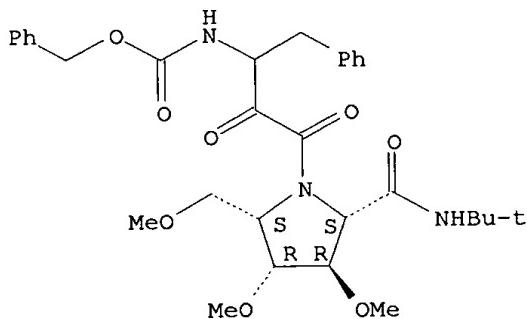
Absolute stereochemistry.





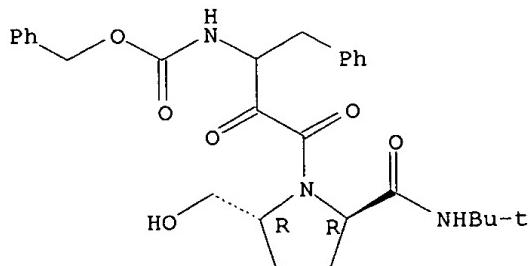
RN 191850-61-0 HCAPLUS
 CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-3,4-dimethoxy-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191850-91-6 HCAPLUS
 CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-5-(hydroxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2R-(2.alpha.,5.beta.)]-[partial]- (9CI) (CA INDEX NAME)

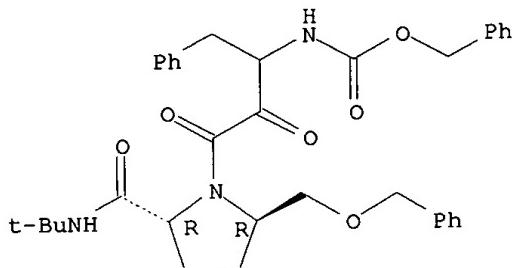
Absolute stereochemistry.



RN 191850-92-7 HCAPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-5-[(phenylmethoxy)methyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2R-(2.alpha.,5.beta.)]-[partial]- (9CI) (CA INDEX NAME)

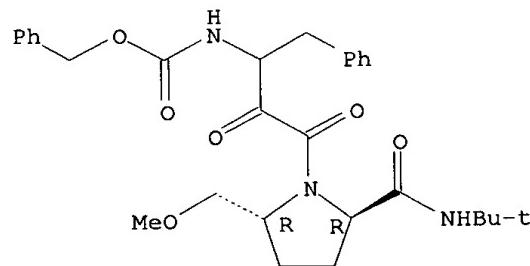
Absolute stereochemistry.



RN 191850-93-8 HCPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2R-(2.alpha.,5.beta.)]-[partial]- (9CI) (CA INDEX NAME)

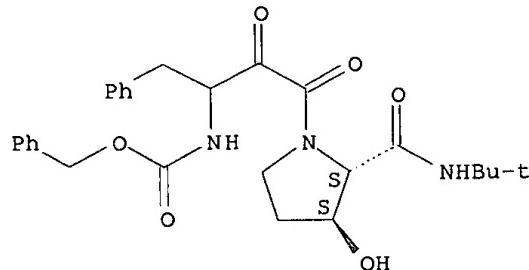
Absolute stereochemistry.

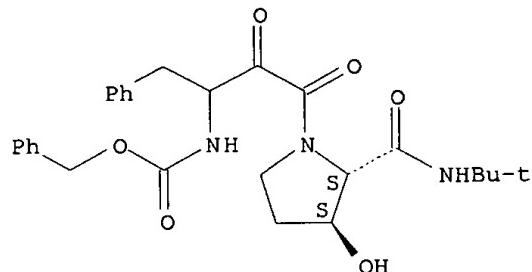


RN 191850-94-9 HCPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-3-hydroxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2S-(2.alpha.,3.beta.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

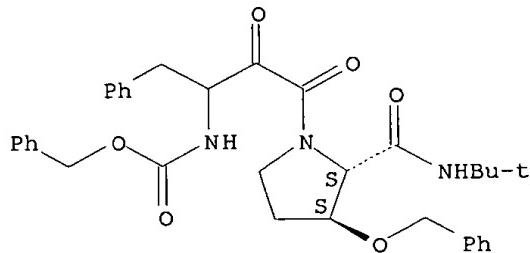




RN 191850-95-0 HCPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-3-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2S-(2.alpha.,3.beta.)]-[partial]- (9CI) (CA INDEX NAME)

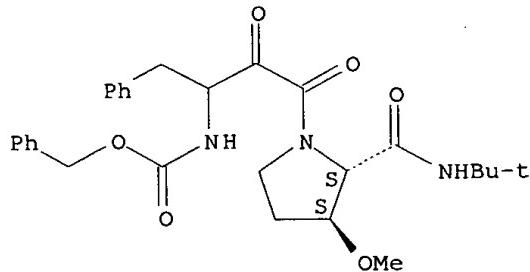
Absolute stereochemistry.



RN 191850-96-1 HCPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-3-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2S-(2.alpha.,3.beta.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

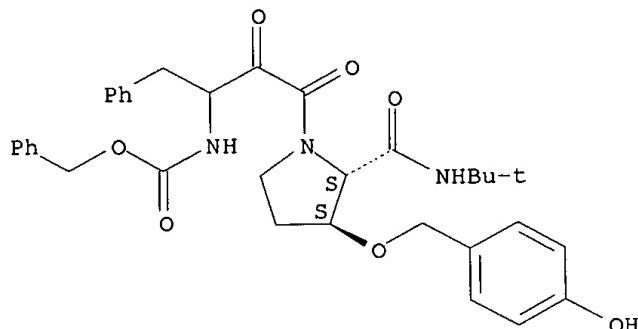


RN 191851-37-3 HCPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-3-[(4-hydroxyphenyl)methoxy]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2S-(2.alpha.,3.beta.)]-[partial]- (9CI) (CA INDEX NAME)

NAME)

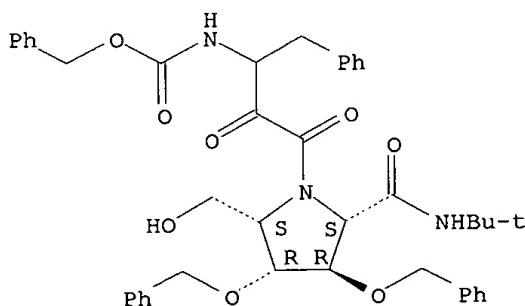
Absolute stereochemistry.



RN 191851-40-8 HCPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-5-(hydroxymethyl)-3,4-bis(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

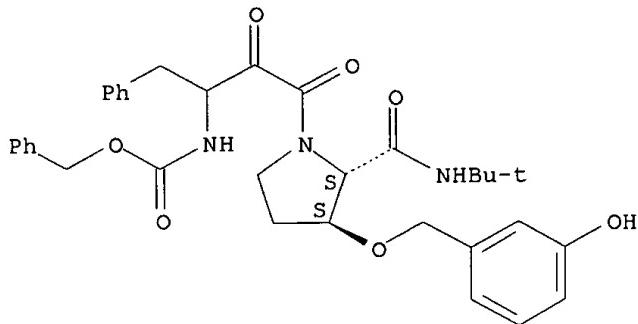
Absolute stereochemistry.



RN 191851-42-0 HCPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-3-[(3-hydroxyphenyl)methoxy]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2S-(2.alpha.,3.beta.)]-[partial]- (9CI) (CA INDEX NAME)

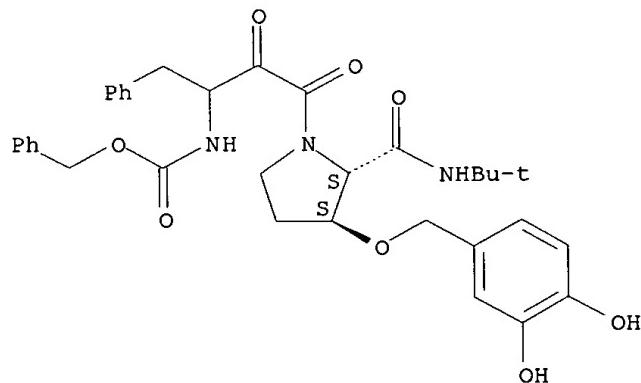
Absolute stereochemistry.



RN 191851-43-1 HCAPLUS

CN Carbamic acid, [3-[3-[(3,4-dihydroxyphenyl)methoxy]-2-[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2S-(2.alpha.,3.beta.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



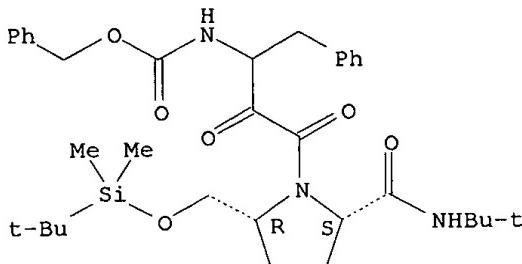
IT 191851-51-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

RN 191851-51-1 HCAPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-5-[(1,1-dimethylethyl)dimethylsilyloxy]methyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2S-(2.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 6 OF 9 HCPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:938815 HCPLUS

DOCUMENT NUMBER: 124:105570

TITLE: Selectivity in the Inhibition of HIV and FIV Protease:
Inhibitory and Mechanistic Studies of
Pyrrolidine-Containing .alpha.-Keto Amide and
Hydroxyethylamine Core StructuresAUTHOR(S): Slee, Deborah H.; Laslo, Karen L.; Elder, John H.; Ollmann, Ian R.; Gustchina, Alla; Kervinen, Jukka; Zdanov, Alexander; Wlodawer, Alexander; Wong, Chi-Huey
CORPORATE SOURCE: Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1995), 117(48), 11867-78

CODEN: JACSAT; ISSN: 0002-7863

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This study describes the development of new pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamine core structures as mechanism based inhibitors of the HIV and FIV proteases. The .alpha.-keto amide core structure is approx. 300-fold better than the corresponding hydroxyethylamine isosteric structure and 1300-fold better than the corresponding phosphinic acid deriv. as an inhibitor of the HIV protease. The .alpha.-keto amide is however not hydrated until it is bound to the HIV protease as indicated by the NMR study and the x-ray structural anal. Further anal. of the inhibition activities of hydroxyethylamine isosteres contg. modified pyrrolidine derivs. revealed that a cis-methoxy group at C-4 of the pyrrolidine would improve the binding 5- and 25-fold for the trans-isomer. Of the core structures prepd. as inhibitors of the HIV protease, none show significant inhibitory activity against the mechanistically identical FIV protease, and addnl. complementary groups are needed to improve inhibition.

IT 141197-75-3P

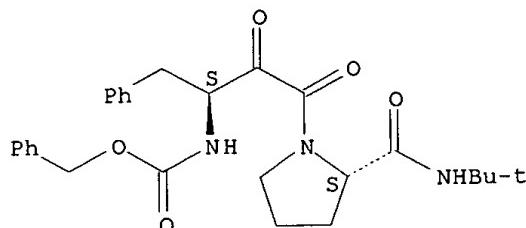
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(HIV and FIV proteases inhibition by pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamines)

RN 141197-75-3 HCPLUS

CN Carbamic acid, [(1S)-3-[(2S)-2-[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



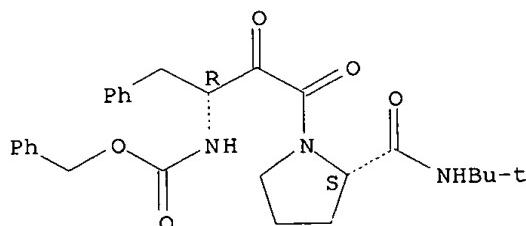
IT 172883-15-7P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HIV and FIV proteases inhibition by pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamines)

RN 172883-15-7 HCAPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [S-(R*,S*)]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



IT 172696-33-2P 172696-34-3P 172823-22-2P

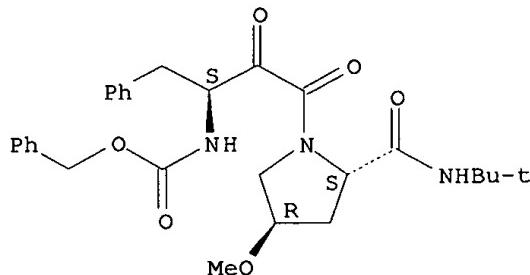
172823-23-3P 172823-24-4P 172823-25-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction with benzyloxycarbonyl chloride)

RN 172696-33-2 HCAPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester,
[2S-[1(R*),2.alpha.,4.beta.]]- (9CI) (CA INDEX NAME)

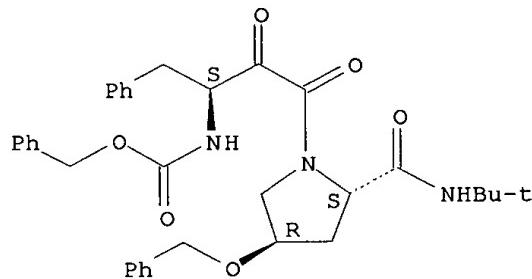
Absolute stereochemistry.



RN 172696-34-3 HCPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2S-[1(R*),2.alpha.,4.beta.]]- (9CI) (CA INDEX NAME)

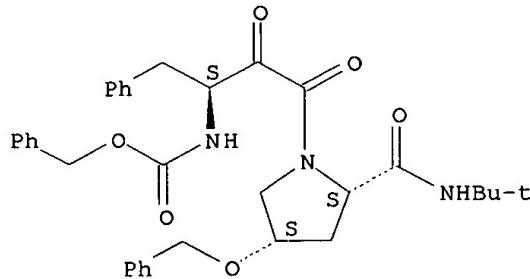
Absolute stereochemistry.



RN 172823-22-2 HCPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2S-[1(R*),2.alpha.,4.alpha.]]- (9CI) (CA INDEX NAME)

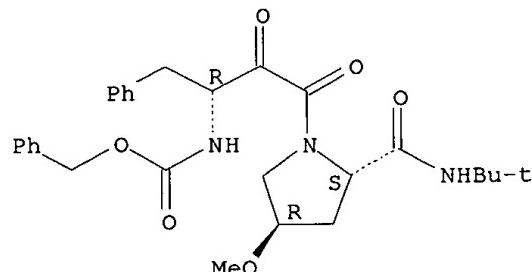
Absolute stereochemistry.



RN 172823-23-3 HCPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester, [2S-[1(S*),2.alpha.,4.beta.]]- (9CI) (CA INDEX NAME)

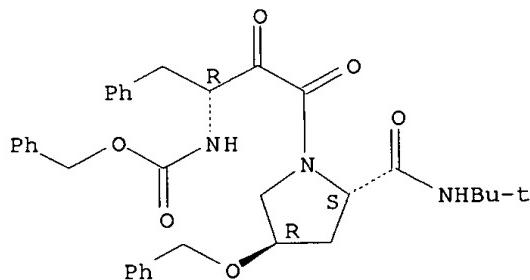
Absolute stereochemistry.



RN 172823-24-4 HCPLUS

CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)aminocarbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(S*),2.alpha.,4.beta.]]- (9CI) (CA INDEX NAME)

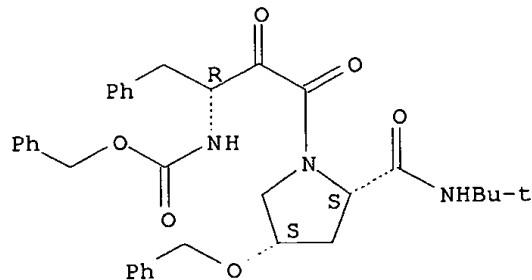
Absolute stereochemistry.



RN 172823-25-5 HCPLUS

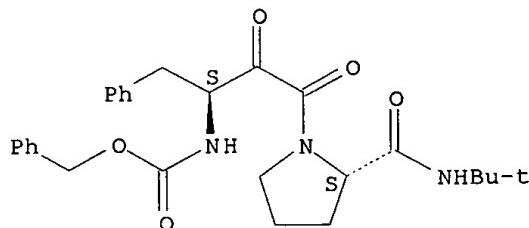
CN Carbamic acid, [3-[2-[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(S*),2.alpha.,4.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1994:289408 HCAPLUS
 DOCUMENT NUMBER: 120:289408
 TITLE: Three-dimensional QSAR of human immunodeficiency virus
 (I) protease inhibitors. 1. A CoMFA study employing
 experimentally-determined alignment rules
 AUTHOR(S): Waller, Chris L.; Oprea, Tudor I.; Giolitti,
 Alessandro; Marshall, Garland R.
 CORPORATE SOURCE: Cent. Mol. Des., Washington Univ., St. Louis, MO,
 63130, USA
 SOURCE: Journal of Medicinal Chemistry (1993), 36(26), 4152-60
 CODEN: JMCMAR; ISSN: 0022-2623
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Comparative mol. field anal. (CoMFA), a 3-dimensional, quant.
 structure-activity relationship (QSAR) paradigm, was used to exam. the
 correlations between the calcd. physicochem. properties and in the vitro
 activities of a series of human immunodeficiency virus (HIV-1) protease
 inhibitors. The training set consisted of 59 mols. from five
 structurally-diverse transition-state isostere classes: hydroxyethylamine,
 statine, norstatine, keto amide, and dihydroxyethylene. The availability
 of x-ray crystallog. data for at least one representative from each class
 bound to the protease provided information regarding not only the active
 conformation of each ligand but also, via superimposition of protease
 backbones, the relative positions of each ligand with respect to one
 another in the active site of the enzyme. Once aligned, these mols.
 served as templates on which addnl. congeners were field-fit minimized.
 Addnl. alignment rules were derived from minimization of the ligands in
 the active site of the semirigid protease. The predictive ability of each
 resultant model was evaluated using a test set comprised of mols. contg. a
 novel transition-state isostere: hydroxyethylurea. Crystallog. studies
 indicated an unexpected binding mode for this series of compds. which
 precluded the use of the field-fit minimization alignment technique. The
 test set mols. were, therefore, subjected to a limited systematic search
 in conjunction with active-site minimization. The conformer of each mol.
 expressing the lowest interaction energy with the active site was included
 in the test set. Field-fit minimization of neutral mols. to crystal
 ligands and active-site minimizations of protonated ligands yielded
 predictive correlations for HIV-1 protease inhibitors. The use of
 crystallog. data in the detn. of alignment rules and field-fit
 minimization as a mol. alignment tool in the absence of direct exptl. data
 regarding binding modes is strongly supported by these results.
 IT 141197-75-3
 RL: BIOL (Biological study)
 (human immunodeficiency virus 1 protease inhibition by, QSAR of)
 RN 141197-75-3 HCAPLUS
 CN Carbamic acid, [(1S)-3-[(2S)-2-[[[(1,1-dimethylethyl)amino]carbonyl]-1-
 pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI)
 (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 8 OF 9 HCPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:245776 HCPLUS

DOCUMENT NUMBER: 120:245776

TITLE: Preparation of cyclic amides of 3-amino-2-hydroxycarboxylic acids as HIV protease inhibitors

INVENTOR(S): Krantz, Alexander; Tam, Tim Fat; Castelhano, Arlindo Lucas; Nestor, John Joseph, Jr.

PATENT ASSIGNEE(S): Syntex (U.S.A.), Inc., USA

SOURCE: PCT Int. Appl., 76 pp.

CODEN: PIXXD2

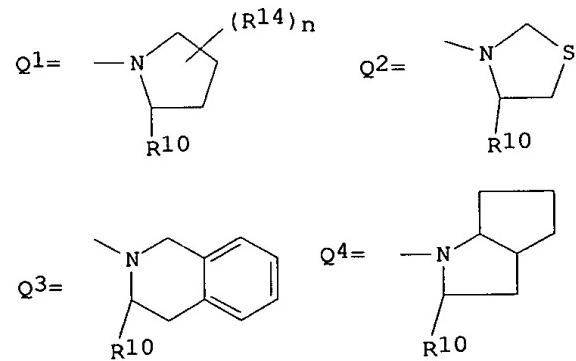
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9313066	A1	19930708	WO 1992-US10772	19921218
W: AU, CA, FI, HU, JP, KR, NO, NZ RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9332782	A1	19930728	AU 1993-32782	19921218
ZA 9209869	A	19940620	ZA 1992-9869	19921218
PRIORITY APPLN. INFO.:			US 1991-812905	19911220
			WO 1992-US10772	19921218
OTHER SOURCE(S):	MARPAT	120:245776		
GI				



AB R1R2NCHR3CONHCHR4CR5R6COR7 [R1 = (ar)alkoxycarbonyl, (substituted) aralkanoyl, aroyl, heterocyclcarbonyl, aryloxyalkanoyl, carbamoyl, heterocyclloxyalkanoyl; R2, R5 = H; R3 = (substituted) alkyl, R4 = (substituted) aryl, aralkyl; R6 = OH; R5R6 = O; R1 = Q1-Q4, etc.; n = 0-2; R10 = alkoxycarbonyl, (substituted) carbamoyl; R14 = OH, alkyl, alkoxy, Ph], were prep'd. Thus, N'-tert-Bu prolinamide (prepn. given) was coupled with (2S,3S)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid using EDCI/hydroxybenzotriazole in DMF to give 1-[(2S,3S)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-N'-tert-butyl-L-prolinamide. I inhibited HIV protease with IC₅₀ = 0.49-30 nM. I dosage formulations are given.

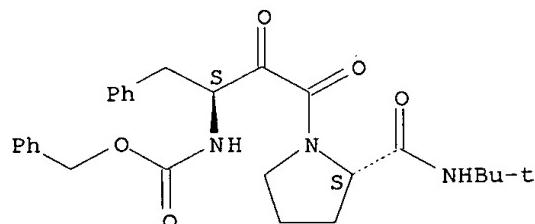
IT 141197-75-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as HIV protease inhibitor)

RN 141197-75-3 HCPLUS

CN Carbamic acid, [(1S)-3-[(2S)-2-[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl-, phenylmethyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 9 OF 9 HCPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1992:227702 HCPLUS

DOCUMENT NUMBER: 116:227702

TITLE: Intriguing structure-activity relations underlie the potent inhibition of HIV protease by norstatine-based peptides

AUTHOR(S): Tam, Tim F.; Carriere, Julie; MacDonald, I. David; Castelhano, Arlindo L.; Pliura, Diana H.; Dewdney, Nolan J.; Thomas, Everton M.; Bach, Chinh; Barnett, Jimmy; et al.

CORPORATE SOURCE: Syntex Res. Canada, Mississauga, ON, L5N 3X4, Can.

SOURCE: Journal of Medicinal Chemistry (1992), 35(7), 1318-20
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Phenylnorstatine contg. peptides extending from the P2 to P1' positions, with L-proline at the P1' position and S-stereochem. of the P1 component, exhibit impressive potency vs. HIV-1 potease (IC₅₀ = 0.58-7.4 nM). Representative ketoamides are also active with slightly lower potency. Analogous hydroxyethylamines have previously been reported to be potent inhibitors of this enzyme. The presence of an addnl. carbonyl in this series of proline-based inhibitors enhances their potency, and alters

structure-activity relations profoundly. Whereas divergent effects on potency have been obsd. for epimeric hydroxyethylamines upon extension of such P1' terminal peptides to P3' with Ile-Val, lengthening of norstatine contg.-inhibitors in the same fashion, dramatically increases the potency of the R-diastereomer and leaves the IC50 of the S-epimer essentially unchanged. Most interestingly, amino acid residues in the P1' position contg. parent and fused piperidines lower activity in the norstatine series. By contrast, significant enhancements in inhibitor potency were reported in the hydroxyethylamine series for such proline replacements. Conformational preferences of 6 member rings influenced by A1,3-strain may contribute to the redn. in potency obsd. for the norstatine contg. peptides.

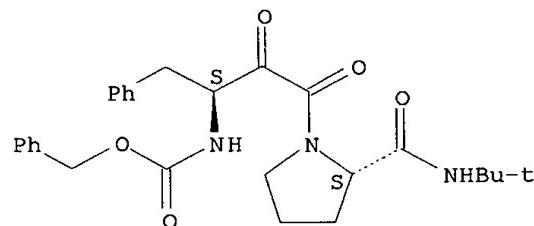
IT 141197-75-3

RL: BIOL (Biological study)
(human immunodeficiency virus 1 protease inhibition by)

RN 141197-75-3 HCPLUS

CN Carbamic acid, [(1S)-3-[(2S)-2-[[((1,1-dimethylethyl)amino)carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



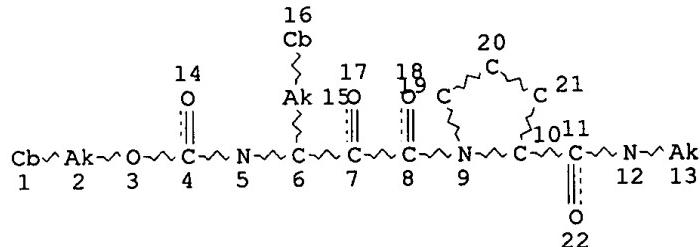
Meller 09/077,712

February 11, 2003

=> d que 17

L1

STR



NODE ATTRIBUTES:

CONNECT IS E2 RC AT 2
CONNECT IS E2 RC AT 5
CONNECT IS E2 RC AT 12
CONNECT IS E1 RC AT 13
CONNECT IS E2 RC AT 15
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GGCAT IS MCY UNS AT 1
GGCAT IS LIN LOC SAT AT 2
GGCAT IS LIN LOC SAT AT 15
GGCAT IS MCY UNS AT 16
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E6 C AT 1
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GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 22

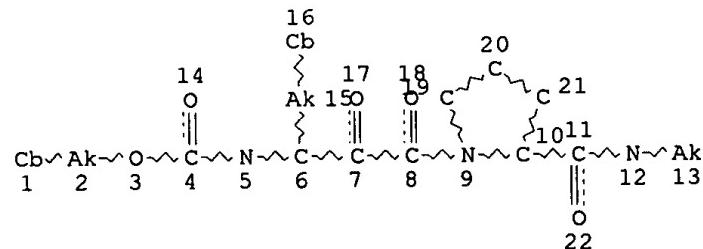
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=> d que 19

L1

STR



NODE ATTRIBUTES:

CONNECT IS E2 RC AT 2
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CONNECT IS E2 RC AT 12
CONNECT IS E1 RC AT 13
CONNECT IS E2 RC AT 15
DEFAULT MLEVEL IS ATOM
GGCAT IS MCY UNS AT 1
GGCAT IS LIN LOC SAT AT 2
GGCAT IS LIN LOC SAT AT 15
GGCAT IS MCY UNS AT 16
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E6 C AT 1
ECOUNT IS E6 C AT 16
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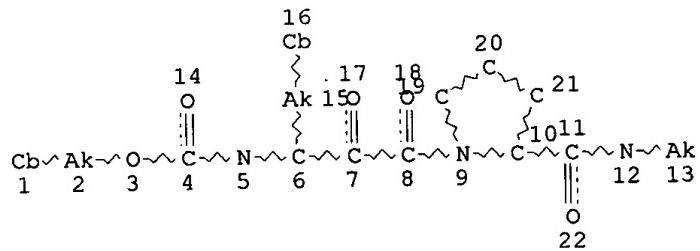
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=> d que 111

L1 STR



NODE ATTRIBUTES:

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CONNECT IS E2 RC AT 5
CONNECT IS E2 RC AT 12
CONNECT IS E1 RC AT 13
CONNECT IS E2 RC AT 15
DEFAULT MLEVEL IS ATOM
GGCAT IS MCY UNS AT 1
GGCAT IS LIN LOC SAT AT 2
GGCAT IS LIN LOC SAT AT 15
GGCAT IS MCY UNS AT 16
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E6 C AT 1
ECOUNT IS E6 C AT 16
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GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE

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Meller 09/077,712

February 11, 2003

L10
L11

TRANSFER PLU=ON L3 1-40 CN : 44 TERMS
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